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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/813,341	03/20/2001	Kathy L. Miller	P1780R1	1230

7590 03/27/2003

Attn: Wendy M. Lee
1 DNA Way
South San Francisco, CA 94080-4990

EXAMINER
YU, MISOOK

ART UNIT	PAPER NUMBER
1642	15

DATE MAILED: 03/27/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/813,341	MILLER ET AL.	
	Examiner	Art Unit	
	MISOOK YU, Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 January 2002 and 25 February 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-15 and 17-80* is/are pending in the application.

4a) Of the above claim(s) *3,10,17-20,27-32,43-56,67,70-74 and 79* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4-9,11-15,21-26,33-42,57-66,68,69,75-78 and 80* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *4-7, 14* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Comply to sequence rules* .

DETAILED ACTION

Election/Restrictions

Applicant's election of group VII drawn to antibody to DR5 in Paper No. 13 and Applicant's election of species, four binding sites, VH-CH1-VH-CH1, SEQ ID NO:10 in Paper No. 14 are acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)). Claims 1-15, and 17-80 are pending. Claims 17-20, 27-32, 43-56, 70-72 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim and Claim 3, 10, 67, 73, 74, and 79 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected species, there being no allowable generic or linking claim. Election was made **without** traverse in Paper No. 12 and in Paper No. 14. Claims 1, 2, 4-9, 11-15, 21-26, 33-42, 57-66, 68, 69, 75-78, and 80 are examined to the extent as they are drawn to elected species. Since applicant has received two restriction requirements already, the Office examines the elected claims although the instantly elected claims as written present two inventions with two sets of generic claims to the Office action, which in turn has put serious burden on the Office (see the art rejection below and the volume of IDS applicant has supplied for the Office to consider, close to 300 journal articles and patent documents); first invention is a general methodology of making tetravalent antibody comprising an FC region and four antigen binding sites amino-terminal to Fc; the second invention is an antibody to DR5. The Office acknowledges applicant's request to rejoin the linking claims if the species are allowable. If the elected species are allowable, then the search will be extended to determine if the generic claims are allowable. However, since the species are not allowable over art (see art rejections below), the Office does not expand the search.

Specification

This application contains sequence disclosures, for example in claim 11, and Figure 3 that are encompassed by the definitions for nucleotide and/or amino acid sequences set

forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth below or on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures. 37 CFR 1.821(a) presents a definition for "nucleotide and/or amino acid sequences." The instant application contains an unbranched specifically defined sequence of more than ten nucleotides. Nucleotide and/or amino acid sequences as used in 37 CFR 1.821 through 1.825 are interpreted to mean an unbranched sequence of four or more amino acids or an unbranched sequence of ten or more nucleotides. Branched sequences are specifically excluded from this definition. Sequences with fewer than four specifically defined nucleotides or amino acids are specifically excluded from this section. "Specifically defined" means those amino acids other than "Xaa" and those nucleotide bases other than "n" defined in accordance with the World Intellectual Property Organization (WIPO) Handbook on Industrial Property Information and Documentation, Standard ST.25: Standard for the Presentation of Nucleotide and Amino Acid Sequence Listings inPatent Applications (1998), including Tables 1 through 6 in Appendix 2 (see MPEP § 2422).

Claim Objections

Claims 21-26, 33-42, and 69 are objected because the claims have not amended to reflect the election (Paper No. 11). The claims are still drawn to multiple inventions instead of the elected invention, i.e., antibody to DR5. Appropriate correction is required. For the purpose of this Office action, the Office will examine the claims to the extent they read on DR5. However, this treatment does not relieve applicant the burden of responding to this objection.

Claim 11 is objected to because of the following informalities: it depends on claim 10, which is not examined because it does not fall on the first elected species of the linking pattern, VH-CH1-VH-CH1- Fc region. Applicant elected the tandem Fd fragments without the flexible linker as the first species, therefore claim 11 does not read on the first species. See Paper No. 13. Appropriate correction is required. As for the purpose of this office action, the limitation of claim 11 with respect to the generic

claim will be examined. However, this treatment does not relieve applicant the burden of responding to this objection.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 62-65 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 62 recites "a CH4 domain" but it is not clear what the metes and bounds are.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1, 2, 4- 6, 8, 11-15, 66, 68, 75, 76, 80 are rejected under 35 U.S.C. **102(a)** as being anticipate by Santos et al (Clin Cancer Res. 1999 Oct;5(10 Suppl):3118s-3123s).

The claims are interpreted as drawn tetravalent (four antigen binding sites), monospecific (claim 15) comprising an Fc region and four binding sites amino-terminal

to the Fc region. Santos et al teach monospecific tetravalent (four antigen binding sites) comprising an Fc region and four binding sites amino-terminal to the Fc region. Note the entire article, especially Fig. 1 and abstract. As for the instant claim 11, Santos et al also teach Gly-Ser linker at the abstract. See the line 7 from bottom of the abstract. As for the limitation, "cytotoxic agent" in claim 80, Santos et al also teach radiolabel at line 3 of the abstract. As for claims 12 -14, the Office does not have the facilities and resources to provide the factual evidence needed in order to establish that the composition of the prior art does not possess the same material, structural and functional characteristics of the instantly claimed composition. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed composition is different from those taught by the prior art and to establish patentable differences. See In re Best 562F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray 10 USPQ 2d 1922 (PTO Bd. Pat. App. & Int. 1989).

Claims 1, 2, 4- 6, 8, 12-14, 66, 75, 76, are rejected under 35 U.S.C. **102(a)** as being anticipate by Alt et al (FEBS letters, Jul 2 1999, vol. 454, p90-4).

The claims are interpreted as drawn to tetravalent (four antigen binding sites) comprising an Fc region and four binding sites amino-terminal to the Fc region. Alt et al teach tetravalent (four antigen binding sites) comprising an Fc region and four binding sites amino-terminal to the Fc region. Note the entire article, especially Fig. 1 and abstract. As for claims 12 -14, the Office does not have the facilities and resources to provide the factual evidence needed in order to establish that the composition of the prior art does not possess the same material, structural and functional characteristics of the instantly claimed composition. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed composition is different from those taught by the prior art and to establish patentable differences. See In re Best 562F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray 10 USPQ 2d 1922 (PTO Bd. Pat. App. & Int. 1989).

Claims 57-66, 68, 75-78,and 80 are rejected under 35 U.S.C. **102(e)** as being anticipated by US Pat 6,066,719 (IDS, May 23, 2000). The claims are interpreted as drawn to protein (more specifically antibody) with the elected species of the linking pattern, VH-CH1-VH-CH1 with attached dimerization domain. US Pat 6,066,719 teach a protein with VH-CH1-VH-CH1 with hinge region as attached dimerization domain. Note the entire document, especially the front page, claims 1-10. As for claim 64, the patent teaches at column 11 line 57 that leucine zippers are used as dimerization domaim. As for claim 80, the patent teaches cytotoxic agent at column 15 lines 8-15.

Claims 21-26 are rejected under 35 U.S.C. **102(b)** as being anticipated by WO 98/41629 (IDS, 24 September 1998).

The claims are interpreted as drawn to antibody to DR-5 in light of the election (note Paper No.11). WO 98/41629 teaches antibody to DR5 (see page 36 lines 25 to page 37 lines 5, claims 21, 25, 26) and also teaches agonist antibody useful for treating cancer and other proliferative diseases at page 37 line 5, page 38 lines 31-35.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claim 7 is rejected under 35 U.S.C. **103(a)** as being unpatentable over Santos et al (cited supra) as applied to claim 1 and 8 above and further in view of US Pat 6,066,719 (cited supra).

The claim is interpreted as drawn to tetravalent (four antigen binding sites), comprising an Fc region and four binding sites amino-terminal to the Fc region with VH-CH1-VH-CH1-Fc linking pattern. Santos et al teach tetravalent (four antigen binding

sites), comprising an Fc region and four binding sites amino-terminal to the Fc region. Santos et al teach tetravalent antibody with Fv, not the tandem repeat of Fd. However, US Pat 6,066,719 teach another way of making tetravalent antibody is VH-CH1-VH-CH1-Fc, such that Fc is used as dimerization domain. VH-CH1-VH-CH1-Fc resembles more close to human immuonglobulin than tetravalent made with Fv only, Therefore, it would have been obvious to one having ordinary skill in the art at the time the claimed invention was made to make the tetravalent antibody with reasonable expectation of success in order to test if it has better avidity for a specific antigen, especially in cancer treatment area.

Claim 9 is rejected under 35 U.S.C. **103(a)** as being unpatentable over of Santos et al above as applied to claims 1 and 8 above and further in view of US Pat 6,066,719 (cited supra).

The claim is interpreted as drawn tetravalent (four antigen binding sites), comprising an Fc region and four binding sites amino-terminal to the Fc region, further comprising CL domain. US Pat 6,066,719 teach method of making tetravalent recombinant antibody with CL domain. Therefore, it would have been obvious to one having ordinary skill in the art at the time the claimed invention was made to make tetravalent recombinant antibody further comprising CL domain with reasonable expectation of success since adding the domain is one variation of many different ways of making recombinant multivalent antibody especially if one in ordinary skill would like to make multivalent antibody as shown at the front page of the patent since the CL domain pairs with heavy chain to correctly folded antigen binding sites.

Claims 33-42 are rejected under 35 U.S.C. **103(a)** as being unpatentable over WO 98/41629 as applied to claims 21-26 above and further in view of either US Pat 6,066,719 (cited supra) or Santos et al above (cited supra).

The claims are interpreted as recombinant tetravalent (four binding sites, note the election) antibody capable of binding DR5. WO 98/41629 teaches antibody to DR5 as explained above. Although the primary reference does not specifically discloses

tetravalent recombinant DR5 antibody, either US Pat 6,066,719 or Santos et al teach making tetravalent recombinant antibody to a specific protein, once the protein sequence is known, is a routine procedure in the art. Further, either US Pat 6,066,719 or Santos et al teach that antibody with four binding sites may have higher avidity for the antigen, see for example Fig. 4 of Santos et al. Therefore, it would have been obvious to one having ordinary skill in the art at the time the claimed invention was made to make tetravalent recombinant DR5 antibody with reasonable expectation of success to have higher avidity antibody as well as easy purification purpose.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 57-62, 65 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 5 of U.S. Patent No. 6,066,719. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims are drawn to a generic antibody comprising VH-CH1-VH-CH1-hinge region and the antibody of claim 5 in the patent is drawn to an antibody comprising VH-CH1-VH-CH1-hinge region capable of binding to CD18 and Her2.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MISOOK YU, Ph.D. whose telephone number is 703-308-2454. The examiner can normally be reached on 8 A.M. to 5:30 P.M., every other Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony C Caputa can be reached on 703-308-3995. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Misook Yu
March 20, 2003

ANTHONY C. CAPUTA
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600